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| 09/831,805 | 05/10/2001 | Henry Yue | PF-0643 USN | 9732 |

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| EXAMINER |
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HADDAD, MAHER M

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| ART UNIT | PAPER NUMBER |
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1644

DATE MAILED: 12/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/831,805

Applicant(s)

YUE ET AL.

Examiner

Maher M. Haddad

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 August 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21-44 is/are pending in the application.
- 4a) Of the above claim(s) 23,25-31 and 34-44 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21-22, 24 and 32-33 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10/14/03 6) ☐ Other: _____

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DETAILED ACTION

1. Claims 21-44 are pending.
2. Applicant's election with traverse of Group 6, claims 1-2 and 15 (now claims 21-22, 24 and 32-33) drawn to a purified polypeptide comprising SEQ ID NO: 6 and fragments thereof filed on 8/21/03, is acknowledged.

While Applicant identifies newly added claims 21, 22, 23, and 28-29 as readable on the elected Group 6, however, after a closer look the Examiner identifies newly added claims 21-22, 24 and 32-33 correspond to canceled claims 1, 2 and 15. Further, applicant's election of a species was not part of the Restriction requirement mailed 5/21/03.

Applicant's traversal is on the grounds that the entire restriction requirement be reconsidered because the present application is a national phase application under 37 C.F.R. § 371 and no unity of invention issue was raised during prosecution of original claims 1-20 in the PCT application by either the International Search Authority or the International Preliminary Examination Authority. This is not found persuasive because Applicant's inventions do not contribute a special technical feature when viewed over the prior art. They do not have a single general inventive concept and so lack unity of invention as set forth in the previous Office Action mailed 5/21/03.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 23, 25-31 and 34-44 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.
4. Claims 21-22, 24 and 32-33 are under examination as they read on a purified polypeptide comprising SEQ ID NO: 6, fragments thereof and a composition thereof.
5. The examiner acknowledges receipt of the IDS filed 10/14/03 and 10/6/03. An initialed copy of all of the properly cited references is attached to the instant office action. However, the references cited in the Search Report of PCT/US99/27566 have been considered, but will not be listed on any patent resulting from this application because they were not provided on a separate list in compliance with 37 CFR 1.98(a)(1). In order to have the references printed on such resulting patent, a separate listing, preferably on a PTO-1449 form, must be filed within the set period for reply to this Office Action.
6. Claim 21 is objected to because of the following informality: the usage of the article "an" in claim 21(b), line 1 is improper. The word "an" should be deleted from claim 21(b), line 1. Correction is required.

7. 35 U.S.C. § 101 reads as follows:

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"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

8. Claims 21-22, 24, and 32-33 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility.

Applicants are directed to the final utility guidelines published Jan. 2001 and corresponding training materials (available on the PTO Website), none of the disclosed uses is a specific and/or substantial use.

The instant application has provided a description of an isolated polypeptide. The instant application does not disclose the biological role of the polypeptide or its significance. The instant specification asserts specific utilities for the claimed invention, for the diagnosis, treatment, or prevention of cancer, immune system disorders and infections (on pages 1, 5, 20, 30-31 and 39-42 in particular). The specification also asserts that the claimed immunoglobulin superfamily proteins (IGFAM) is acknowledged by the Applicants to play a structural role in the control of monocyte migration across epithelium or endothelium to sites of inflammation (see page 4, lines 9-19) and those new members of Ig superfamily, known as JAM are situated at tight junction which occur between adjacent epithelial or endothelial cells. Further, the viral proteins which contain Ig domains identified by the specification to involve in tumorigenic poxvirus *Molluscum contagiosum* (see page 4, lines 19-22), and to mediate adhesive interactions at the synaptic junction (see page 5, lines 18-20), among others.

These utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for (IGFAM). The disclosed polypeptide is said to have a potential function based upon its amino acid sequence similarity to other known proteins. After further research, specific and substantial credible utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete.

The instant situation is directly analogous to that which was addressed in *Brenner V. Manson*, 148 U.S. P. Q. 689 (1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this board interpretation was not the intended definition of "useful" as it appears in 35 U.S. C. § 101, which requires that an invention must have either an immediately apparent or fully disclosed "real world" utility. The instant claims are drawn to a polypeptide of as yet undetermined function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that the IGFAM of the instant application was, as of the filing date, useful for the diagnosis prevention and treatment of cancer, immune system disorders and infections. Until some actual and specific significance can be attributed to the protein identified in the specification as IGFAM, one of ordinary skill in the art would be required to perform additional

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experimentation in order to determine how to use the claimed invention. Thus, there was no immediately apparent “real world” utility as of the filing date.

Further, neither the instant specification nor the art of record identifies even a single disease or disorder which has been shown to be associated with an “IGFAM” of the instant invention. IGFAM has not been shown to be differentially expressed in any disease or disorder, the claimed protein can not be employed in a diagnostic capacity. Further, the “IGFAM” of the instant invention has not been shown to be associated with a particular physiological process which an artisan would wish to manipulate for clinical effect by the administration of that protein.

The amino acids of the instant invention are compounds which share some structural similarity with immunoglobulin (Ig) proteins based on sequence similarity. It is not clear if the protein of the instant application would have the same function in mediating adhesive interactions at the synaptic junction or transmigration of monocytes across endothelial cells. Tsukita et al (Nat Rev Mol Cell Biol. 2(4):285-293, 2001) teach the multifunctional strands in tight junction and that JAM was shown to be involved in cell-cell adhesion/junctional assembly of epithelial/endothelial cells as well as in the extravasation of monocytes through endothelial cells, but our knowledge on its function is still fragmentary (see page 287, 1st col., 2nd ¶). Tsukita et al concluded that the picture of the molecular architecture of tight junctions remains incomplete, and other important constituents need to be identified. Further development of the molecular biology of tight junctions will lead to a better understanding of their functions, not only in normal physiology, but also in disease (page 292, last ¶). Attwood (Science 2000; 290:471-473) teaches that “[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000; 18(1):34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., “Abstract” and “Sequence-based approaches to function prediction”, page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan’s best guess as to the function of the structurally related protein (see in particular “Abstract” and Box 2). Finally, even single amino acid differences can result in drastically altered functions between two proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2).

No single effect of the disclosed IGFAM is ascribed to the claimed protein. Note that while the specification produces the full-length protein recombinantly, no biological activity is established for the full length protein or any of the claimed fragments thereof. As such, further research would be required to identify or research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved would be required. Since the instant specification does not disclose a “real world” use or well established utility for IGFAM, then the claimed invention as disclosed does not meet the requirements of 35 U.S. C. § 101 as being useful.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 21-22, 24, and 32-33 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

Further, besides an isolated polypeptide comprising SEQ ID NO: 6, the specification fails to provide any guidance as to how to make (a) any polypeptide comprising a “naturally occurring” amino acid sequence at least 90% identical to any amino acid sequence of SEQ ID NO:6, (b) any biologically active fragment of any polypeptide having any amino acid sequence of SEQ ID NO: 6, and (c) any immunogenic fragment of any polypeptide having any amino acid sequence of SEQ ID NO: 6 in claims 21-22 and 24; any composition comprising any polypeptide of and (b) or (c) mentioned above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Other than the specific SEQ ID NO: 6 mentioned above, the specification fails to provide any guidance as how to make (a) any polypeptide comprising any naturally occurring amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:6, (b) any biologically active fragment of a polypeptide having an amino acid sequence of SEQ ID NO: 6, and (c) any immunogenic fragment of a polypeptide having an amino acid sequence of SEQ ID NO: 6; any composition comprising any polypeptide of (a), (b) or (c) mentioned above.

The specification discloses a single working example of a polypeptide that is naturally-occurring and has at least 90% identity to SEQ ID NO:6, that is the polypeptide of SEQ ID NO:6. In view of the disclosed sequence of SEQ ID NO:6 and its function as immunoglobulin superfamily (IGFAM) protein, the skilled artisan would not be enabled to make and use the immunogenic fragments of SEQ ID NO:6. Furthermore, there is insufficient guidance in the specification as-filed to direct a person of skill in the art as to how to make and use a polypeptide comprising a

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“naturally-occurring” amino acid sequence at least 90% identical to the full length of the sequence of SEQ ID NO:6.

Applicant does not appear to have provided sufficient guidance with respect to “naturally-occurring” polypeptides and how to make and use them. Although the specification does provide some general guidance as to how to isolate other naturally occurring IGFAM using specific anti-IGFAM specific antibodies (e.g., page 54, lines 25-40), it is unpredictable that other “naturally-occurring” polypeptides having IGFAM activity and at least 90% amino acid sequence identity to SEQ ID NO:6 exist.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Applicant does not appear to provide sufficient guidance as to other sources of “naturally-occurring” polypeptides which are at least 90% identical to SEQ ID NO:6 and have IGFAM activity. The state of the art did not recognize other “naturally-occurring” polypeptides that had IGFAM activity and were at least 90% identical to SEQ ID NO:6. Even though the level of skill in the art for isolating “naturally-occurring” polypeptides using antibodies against IGFAM may have been high with respect to the techniques employed, skill in the art does not render the existence of a “naturally-occurring” polypeptide predictable.

The presence of a single working example and the failure of the state of the art either at the time of filing to recognize other “naturally-occurring” polypeptides at least 90% identical to SEQ ID NO:6 indicates that it was highly unpredictable that additional polypeptides meeting these limitation could be isolated, particularly based on the limited guidance provided in the specification as filed. Unlike the fact pattern of In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) where the presence of a hybridoma producing an antibody having the desired properties among the many hybridomas was predictable, in the instant case it is not predictable that other “naturally-occurring” polypeptides at least 90% identical to an amino acid sequence of SEQ ID NO:6 exist. Therefore, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue with respect to other “naturally-occurring” polypeptides at least 90% identical to an amino acid sequence of SEQ ID NO:6 other than SEQ ID NO:6.

The claims as written encompass a broad genus of protein with a large number of possibilities with regard to the length of the amino acid sequence. Further, making changes up to 10% of an amino acid sequence does not provide maintaining the same three dimensional structure as the 100% identity *over the full length of SEQ ID NO:6*. The instant claim language appears to encompass subsequences. For example, claims 21-22 (c-d) recites an immunogenic fragments and a biologically active fragments. Such recitations do not require that the full length of the amino acid sequence of SEQ ID NO: 6 but rather encompasses any amino acid sequence selected from either the full length of SEQ ID NO: 6 or *any subsequence*. However, the specification does not appear to have provided sufficient guidance as to which subsequences of SEQ ID NO: 6 would share the activity of SEQ ID NO:6. Neither does applicant appear to have provided any working examples of any subsequences. Thus it would require undue experimentation of the skilled artisan to determine which subsequences of SEQ ID NO:6 would have the biologically

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active fragments of the full length molecule. Moreover, the number of changes encompassed by “at least about 90% identity” are numerous that it would still require undue experimentation of the skilled artisan to make these changes and then identify which polypeptides.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

11. Claims 21-22, 24, and 32-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of SEQ ID NO: 6.

Applicant is not in possession of (a) any polypeptide comprising a “naturally occurring” amino acid sequence at least 90% identical to any amino acid sequence of SEQ ID NO:6, (b) any biologically active fragment of any polypeptide having any amino acid sequence of SEQ ID NO: 6, or (c) any immunogenic fragment of any polypeptide having any amino acid sequence of SEQ ID NO: 6 in claims 21-22 and 24; any composition comprising any polypeptide of and (b) or (c) mentioned above.

Applicant has disclosed only SEQ ID NO: 6; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. However, to satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563. The written-description requirement can be satisfied “by describing the invention, with all its claimed limitations, not that which makes it obvious,” and by using “such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention.” *Lockwood*, 107 F.3d at 1572. The court said that “an adequate written description of a DNA ... ‘requires a precise definition, such as by structure, formula, chemical name, or physical properties.’ Not a mere wish or plan for obtaining the claimed chemical invention.” *Eli Lilly*, 119 F.3d at 1566 (quoting *Fiers*, 984 F.2d at 1171). Likewise, Applicant fails to satisfy the written-description requirement where the claimed invention called for a “naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:6” and “a polypeptide having an immunogenic/biologically active fragment” of SEQ ID NO: 6, but did not disclose such “variants” and “fragments”. The court stated that “an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, what is required is a description of the DNA itself.” *Fiers* 984 F.2d at 1170.

Consequently, the “naturally occurring” at least 90% identical to an amino acid sequence of SEQ ID NO:6, language in the claims is analogous to the claims found in *Lilly* and *Fiers* because the

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claimed polypeptides are defined only by their homology to SEQ ID NO:6, which is insufficient to satisfy 112(1) since "a mere wish or plan" for obtaining an invention is not enough to comply with 112(1). Furthermore, there is no described or art-recognized correlation or relationship between the structure of the claimed invention, the IGFAM protein and their functions, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of fragments and polypeptide that have at least 90% sequence identity of SEQ ID NO: 6.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed fragments and polypeptides that have at least 90% sequence identity of SEQ ID NO:6. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
December 29, 2003


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